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DETERMINATION OF WOUND BLOOD FLOW IN THE THERMALLY INJURED SOLD--ETC(U)  
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Extensive thermal injury is one of the most severe stresses experienced by individuals in contemporary society. Metabolic, circulatory, and thermoregulatory alterations characterize the major compensatory adjustments following injury and, to a large extent, determine the survival potential of the patient. The initial response to injury, termed "burn shock," usually lasts 24-48 hours and is associated with a marked depression in the patient's metabolic rate, body temperature, and circulation. Following successful resuscitation, the patient gradually becomes hypermetabolic and febrile. These increases in body temperature and metabolism vary with the extent of injury, reach a peak within the first two weeks, and then slowly return to normal with wound coverage and healing. Since these metabolic and thermoregulatory adjustments have been well documented by Wilmore and colleagues (1-4), the intent of these experiments is to characterize the associated cardiovascular changes which occur with thermal injury. Particular emphasis is placed on wound blood flow to include factors involved in its regulation, and the impact of wound perfusion on the total circulatory status of the burn patient.

Acute loss of blood volume precipitates the initial burn shock phase of injury (5). During this phase, the patient becomes hypotensive and cardiac output drops below normal. With volume expansion and increased total peripheral resistance, blood pressure returns toward normal, and cardiac output begins to recover. After 24-48 hours, blood pressure stabilizes at a normal level but cardiac output continues to climb, associated with a progressive increase in plasma volume and decreasing peripheral resistance. The extent of this rise in total body

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circulation is generally related to the size of the surface wound and may reach levels 2-3 times normal in the more extensively injured patients. The magnitude of this circulatory response is best appreciated in the sleeping patient when the level of activity reflects the minimal requirements for life. Typically, a patient with a 50% total body surface wound will, in this basal state, maintain a heart rate of 120-140/min and a cardiac index in excess of  $7 \text{ L/m}^2 \cdot \text{min}$  (6). For normal uninjured persons to generate comparable levels of total body blood flow, they would have to work at roughly one half of their aerobic capacity. For most people, this would correspond to a good brisk jog. While the well trained athlete may do this amount of exercise for several hours each day, the burn patient must sustain this hyperdynamic circulation for at least several weeks. The exact time course of this circulatory response to thermal injury has not been well defined but presumably follows a course similar to metabolism and body temperature and returns toward normal with wound healing.

Gump and associates (7), in 1970, were the first to partition this extra blood flow. They noted that, as in exercise, the resting cardiac index of burn patients was linearly related to oxygen consumption but, at every level of aerobic metabolism, burn patients had higher cardiac outputs than other febrile surgical patients. They also found that splanchnic blood flow in three severely burned patients was slightly increased but represented a smaller portion of the cardiac output than it did in normals or patients with postoperative infection. From this, they concluded that a large portion of the increased cardiac output of burn patients was directed to the periphery.

Later, Wilmore, et al (3), provided additional indirect evidence to suggest that most of the extra peripheral circulation was directed to the body surface. They found that burn patients maintained above-normal surface temperatures despite increased evaporative cooling of the wound and concluded that this elevated skin temperature could be the result of increased superficial blood flow. Additional support for this thesis was provided by demonstrating that the coefficient of core-to-skin heat conductance, an index of skin blood flow, was twice normal in burned patients. Although these indirect measurements did suggest an increase in superficial blood flow in burn patients, the influence of the burn wound on the distribution of this elevated peripheral blood flow remained unknown. To address this problem, a series of studies were designed to measure peripheral blood flow in injured and uninjured limbs of burn patients and to partition this flow into that directed to the burn wound, normal skin, and resting skeletal muscle of the limbs.

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## MATERIALS AND METHODS

### Subjects

Over 60 thermally injured patients were studied. The size of injury ranged from 3-86% of the total body surface. Patients selected for study were 1) from 15 to 55 years of age and free of any disease prior to injury; 2) normotensive and hemodynamically stable after an uneventful resuscitation; 3) in a normal state of hydration with a hematocrit greater than 33, and without abnormalities in serum electrolyte concentration, osmolality, or pH; 4) free of systemic infection as determined by clinical symptoms and signs and daily blood cultures; 5) 6-27 days postinjury, after removal of the eschar, and before significant healing had occurred.

The wounds were treated by a variety of techniques. Most patients were treated by the exposure method and received topical applications of a silver sulfadiazine cream (Silvadene cream) to the injured surface, but several patients were treated with 11% mafenide acetate topical antibiotic (Sulfamylon cream). Some wounds were covered with dressings soaked in saline, 5% mafenide-saturated dressings, or 0.5% silver nitrate; two were treated with cutaneous allograft biological dressings. Although the effects of these treatments on limb blood flow are unknown, they do involve considerable manipulation of the patient, often resulting in discomfort. Therefore, to insure that each subject was well rested for the study, such procedures were minimized for at least 8 hours prior to the study.

### Study Design

Two basic studies were performed. In the first, total limb blood flow was measured by a specially designed venous occlusion plethysmograph. In the second study, resting skeletal muscle blood flow was determined by a standard clearance technique.

The experiments designed to measure leg blood flow took place in an environmental chamber described previously (3). Room temperature was maintained at 30°C, and relative humidity ranged between 40 and 50%. Control subjects were studied in shorts or shorts and halter, and patients were similarly draped with light cotton towels. The post-absorptive subject was moved to the study room in the early morning and placed in bed. Water was given on request and, in some patients, intravenous infusion of 0.04 M sodium chloride solution was maintained to insure normal hydration. Nine copper-constantan thermocouples were attached to the skin at the same sites for all subjects (dorsum of foot, lateral and posterior calf, posterior and anterior thigh, dorsum



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of hand, forearm, abdomen, and low back). Leg skin temperatures were monitored from both legs, using five additional thermocouples, in patients with asymmetric leg burns. In those patients treated in dressings, the thermocouples were placed on the wound under the dressing. A rectal probe was inserted to a depth of 10 cm from the external anal sphincter. Rectal and total body mean skin temperatures were monitored at 5-minute intervals throughout the study to insure that subsequent manipulation of the subject had no appreciable effect on body temperature.

After the subject had rested quietly for at least one hour, the steady-state mean leg skin temperature was determined for the left leg, and the thermocouples were removed. This leg was then inserted into a soft pliable, water-impermeable boot and placed in a full-length plethysmograph. Water was added to the plethysmograph at a temperature equal to the predetermined mean leg skin temperature and maintained at this temperature throughout a 30-minute equilibration period and the following 8-10 blood flow measurements. Setting water temperature equal to that of the leg surface when exposed to the air maintained comparable rates of heat exchange across the limbs while in the plethysmograph and prevented either transient or prolonged changes in body temperature during leg blood flow measurements. A 2- to 3-minute interval separated the blood flow determinations.

The validity (8), simplicity, and noninvasive character of venous occlusion plethysmography make this the optimal approach to the study of peripheral blood flow in critically injured patients. The plethysmograph used in this study, a rigid, rectangular box made of clear plexiglass, is illustrated in Fig. 1. To facilitate its use in injured limbs, it can be disassembled into three sections, a thigh plate and attached boot, a trough section with mesh sling to support the leg, and a full length top. The patient's leg was slipped through a tailor made opening in the thigh plate and into a large loose fitting, polyvinyl boot. The boot served to form a freely expandable, watertight seal between the limb and the plethysmograph, preventing fluid exchange across the burn wound and minimizing contamination. The boot and thigh plate were advanced to the proximal thigh and the leg placed in the mesh sling of the plethysmograph. The three sections of the plethysmograph were then locked together and the box filled with water equal to the mean skin temperature of the leg under study.

Venous occlusion was accomplished by rapid inflation of a 10 centimeter wide tourniquet cuff placed as high on the upper thigh as possible. Occlusion pressure was varied for each subject to obtain a

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maximal rate of limb swelling. With venous occlusion, the limb swells, and the change in limb volume causes water to rise in a chimney located on top of the plethysmograph. The increase in column hydrostatic pressure is converted to an electrical signal, amplified and recorded.

The plethysmograph was calibrated periodically with the leg in place. The volume of the limb within the plethysmograph was determined by subtracting the volume of water in the plethysmograph from its known capacity. The eight to 10 flow measurements were averaged and leg blood flow expressed in ml/100 ml leg volume per minute.

In a separate set of experiments, resting skeletal muscle blood flow was determined in 10 burn patients (mean burn size = 42.5% total body surface, range 25.5-82%). The criteria for patient selection were the same as described earlier. All subjects were confined to bed for a minimum of one hour prior to muscle blood flow measurements. The actual studies took place in the Nuclear Medicine Clinic of the hospital where the ambient temperature was 25-27°C. Since this was slightly below thermal neutrality for resting burned patients, patient comfort was achieved by covering them with light cotton blankets. All subjects rested supine throughout the 20-30 minute study. Only those patients who rested quietly during the actual test, without any leg and/or foot movements, were included in this study.

Blood flow in the tibialis anterior muscle of the lower leg was measured by  $^{133}\text{Xe}$  clearance as described by Lassen, et al (9). Basically, radioactive xenon gas ( $^{133}\text{Xe}$ ) is dissolved in sterile 0.9% NaCl solution to a concentration of 0.5-1.0 mc/ml, and 0.1 ml of this solution is injected 1-2 cm into the tibialis anterior muscle through a 25 gauge hypodermic needle. The disappearance of  $^{133}\text{Xe}$  is monitored for 20-30 minutes postinjection by a collimated scintillation probe placed directly over the injection site. Simultaneous measurements were performed on both legs in four control subjects and five patients. Muscle blood flow (MBF) is calculated from the tangent to the logarithmic curve of  $^{133}\text{Xe}$  washout.

$$\text{MBF (ml/100 g muscle}\cdot\text{min)} = \lambda \cdot 100 \cdot \frac{-dQ/dt}{Q(t)}$$

where  $\lambda$  is the partition coefficient for  $^{133}\text{Xe}$  (amount of tracer in one gram of tissue/amount of tracer in one ml blood) and  $\frac{-dQ/dt}{Q(t)}$

describes the clearance rate of  $^{133}\text{Xe}$  relative to the amount present at time  $t$ ; 0.70 was the value utilized for  $\lambda$  in both control subjects and patients.

## RESULTS

Total leg blood flow was essentially normal in the uninjured legs of burn patients (Table 1), but increased in a curvilinear manner with the size of leg burn and approached a plateau of 8.0 ml/100 ml·min as the extent of leg injury exceeded 60% (Fig. 2). Resting skeletal muscle blood flow, however, was normal in burn patients (Table 2).

## DISCUSSION

These leg blood flow measurements(10,11) clearly demonstrated that peripheral blood flow is increased during the hypermetabolic-hyperdynamic phase of thermal injury and strongly suggest that a major portion of this extra blood flow is directed primarily to the burn wound.

Increased wound blood flow was supported by two additional observations. For example, in the third degree wound, which is associated with superficial vascular thrombosis, leg blood flow was near control levels shortly after injury. Neovascularization is a constant feature of wound repair, and the development of granulation tissue in the open wound corresponds structurally with a dense, superficial, vascular bed. With time, therefore, blood flow increased to reach levels predicted from the size of limb burn, presumably associated with the formation of a richly vascularized wound bed. In contrast, partial-thickness injury does not ablate the superficial vascular bed and blood flow was elevated in these limbs as soon as circulatory volume was restored. A second example of increased wound perfusion developed subsequent to leg blood flow measurements before and after excision to fascia of a 82.5% leg surface wound. With the removal of the burn tissue, leg perfusion dropped from 5.27 to 3.33 ml/100 ml·min.

The increased rate of wound perfusion is, in part, responsible for the elevated surface temperatures of these patients. This is most evident in two groups of patients with and without leg burns but with comparable core and total body mean skin temperatures (Table 1). Since these two groups maintained similar levels of body heat content, the higher surface temperatures of the burned legs can only be the result of higher superficial blood flows. Considering the increased evaporative cooling which occurs from the burn wound, the impact of increased superficial blood flow in maintaining an elevated surface temperature is even more impressive.



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These peripheral blood flow measurements in burn patients make it possible to characterize the shift in limb perfusion following thermal injury (Fig. 3). Stolwijk (12) has partitioned resting leg blood flow as follows: 29% to muscle, 46% to skin, and 25% to the remainder. Assuming little or no change in either muscle, fat, or bone perfusion, blood flow to the skin of an unburned leg, in a typical patient with a 50% total body surface burn, increases by no more than 7% above normal. If this same burn patient had a wound covering 50% of his leg, limb blood flow would approach 8 ml/100 ml leg volume per minute. Since the size of limb burn has no effect on resting skeletal muscle blood flow, 80% of total leg flow in this patient would be directed to the surface with the vast majority going to the burn wound.

What are the factors responsible for this redistribution of peripheral blood flow following thermal injury? Leg blood flow in uninjured legs of burn patients is normal, in spite of the elevated rectal temperature. A comparable degree of hyperthermia in resting normal man would result in a 4-5 fold increase in leg blood flow (13). Control levels of blood flow to the uninjured limbs suggest that these febrile patients vasoconstrict normal skin. Since such cutaneous vasoconstriction is an appropriate heat conservation response during fever, why does the wound remain dilated? The selected elevation in wound blood flow cannot be explained by a complete loss of intrinsic vascular smooth muscle tone. This was demonstrated by the capacity of severely burned legs with high basal flows to vasodilate further when limb surface temperature was increased (Fig. 4) (10). The burn wound appears to be "functionally" denervated, however, since it fails to vasodilate when its temperature is held constant and the patient's core temperature elevated 0.4-0.5°C by external heating (Table 3) (14). This loss of neurogenic vasomotor control of the burn wound, when normal skin vasodilates appropriately (Fig. 5), is most likely the combined result of 1) actual physical disruption of sympathetic vasomotor nerves at the time of injury, and 2) the presence of local inflammatory and metabolic factors which interfere with neuromuscular transmission in vessels which retain their innervation. Possible chemical vasodilators identified in the burn wound include such inflammatory products as histamine, kinins, and various prostaglandins (15,16,17). The anaerobic nature of granulation tissue is evident by increased rates of lactate production in the injured extremities (6). This metabolic environment with the associated release of lactate in the wound may also contribute to local vasodilation and interfere with extrinsic vasomotor influences. Actual physical denervation of wound microvasculature is most apparent after inflammation subsides and the wound is completely healed. While local chemistry should approach that of normal skin with wound closure, reflex vasomotor control to



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the healed wound is still markedly reduced. The most likely explanation for this lag in reinnervation of the burn wound is the evidence that regeneration of sympathetic nerves in granulation tissue is slow and vascular reinnervation often incomplete, particularly if split-thickness skin grafts are utilized (18,19).

Regardless of the precise mechanisms responsible for the loss of neural control of wound vasculature, this functional denervation will allow local environmental factors to exert a greater influence on wound perfusion. Consequently, the control of wound circulation becomes less like that of normal skin and more like that of other critical tissues (heart, brain, and active skeletal muscle), the blood flows of which vary as a function of local metabolic conditions rather than as part of integrated total body thermoregulatory or baroreceptor reflexes.

What is the impact of this high obligatory wound blood flow on the distribution of total body circulation in the burn patient? The estimated cardiac index of a "typical" patient with a 50% total body surface burn wound exceeds  $7.0 \text{ L/m}^2 \cdot \text{min}$ . Based on actual measurements of splanchnic (7), limb (10), muscle (11) and renal (unpublished data) blood flow, and assuming no change in brain circulation but a rise in coronary perfusion proportional to change in total flow, one may partition the cardiac index of this hyperdynamic patient (Fig. 6). This estimate describes a general shift in the distribution of total body circulation toward the periphery with the major portion of the extra flow going to the wound. This increase in superficial flow is, however, well within maximum levels of cutaneous flow observed in resting-normal man under severe heat stress (20).

The dominance of local wound effects on the distribution of peripheral blood flow in patients with marked systemic alterations in metabolism and thermoregulation demonstrates the priority of the wound in the body's homeostatic response to injury. High obligatory wound blood flow is the major cause for the marked increase in total body circulation following thermal injury. Our calculations indicate that as much as 50-60% of the extra blood flow is directed to the burn wound. This increased superficial blood flow severely reduces the capacity of the patient to conserve body heat and maintain the febrile state. The associated increase in body heat production necessary to compensate for this insulative defect places additional metabolic demands on the cardiovascular system. In other words, the major portion of the increase in total body circulation either goes directly to the burn wound or develops indirectly as a consequence of the effects of

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this high obligatory wound blood flow on the thermal balance of the patient.

The combined magnitude and duration of these circulatory adjustments to thermal injury represent a severe test of the body's cardiovascular system. The capacity to generate and sustain the required circulatory activity is a major determinant of the patient's ability to survive the initial injury and ultimately heal the wound.

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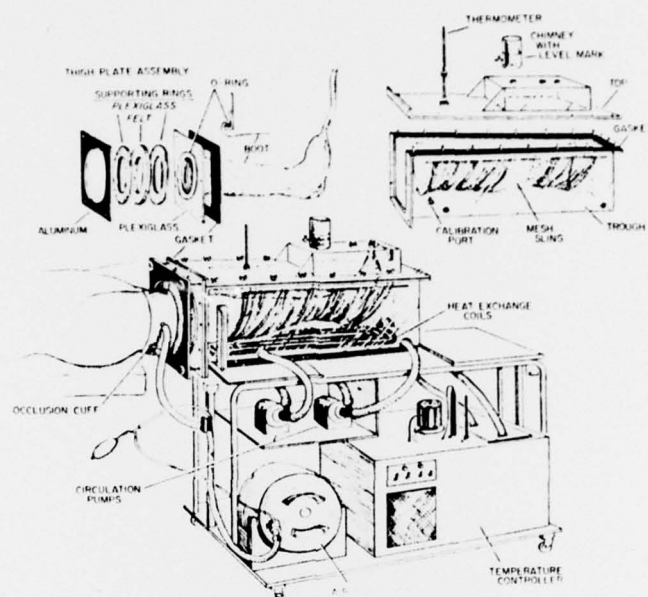


Figure 1. Leg plethysmograph. This design provides a safe, comfortable, noninvasive approach to the study of peripheral blood flow in critically injured patients.

Temperature (°C)	Controls	No Leg Burn	Leg Burn
Rectal	37.0 ± 0.1	37.9 ± 0.2	38.0 ± 0.1
Mean Skin	34.5 ± 0.1	35.4 ± 0.3	35.8 ± 0.2
Mean Leg Skin	33.9 ± 0.2	34.6 ± 0.3	35.4 ± 0.2
Leg Blood Flow (ml/100 ml·min)	2.74 ± 0.16	3.13 ± 0.21	5.89 ± 0.68

Table 1. Local effects of leg burn wound on limb blood flow and surface temperatures.



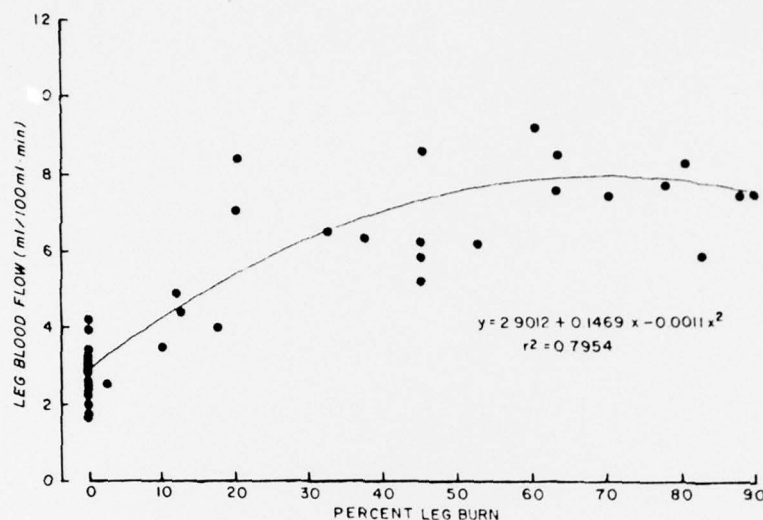


Fig. 2. The effect of local injury on leg blood flow. Leg blood flow increases with the extent of limb burn, suggesting that the extra blood flow is directed to the surface wound.

CONTROLS	3.29 ± 0.24
SMALL LEG BURNS	3.47 ± 0.50
LARGE LEG BURNS	3.57 ± 0.28

Table 2. Resting skeletal muscle blood flow (ml/100 g·min) following thermal injury. The local presence of a burn wound has no effect on muscle perfusion. Values represent group means ± S.E.M.

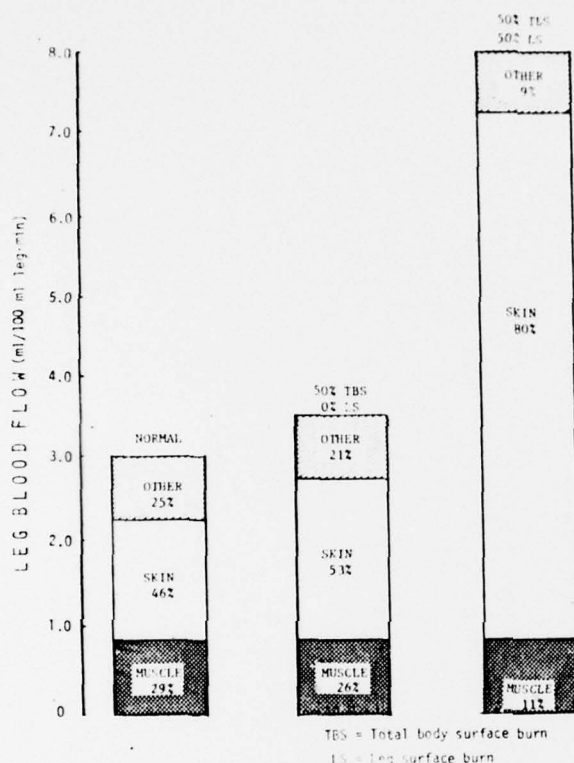


Figure 3. The estimated distribution of peripheral blood flow following a 50% total body surface (%TBS) burn. Leg blood flow is essentially normal in the uninjured limbs (0% LS - % leg surface burn) but increases markedly when 50% of the limb surface is burned (50% LS). The vast majority of this increase in peripheral blood flow is directed to the wound.

SUBJECTS	$\Delta T_{re}$	LEG BLOOD FLOW (ml/100 ml·min)		
		BEFORE	AFTER	% INCREASE
CONTROLS	+ 0.4°C	2.93	4.56	56
SMALL LEG BURNS (0-2.5%)	+ 0.6°C	3.86	6.34	64
LARGE LEG BURNS (37.5-70%)	+ 0.5°C	7.17	7.73	8

Table 3. Changes in leg blood flow following 30 minutes of external heating. Leg surface temperature is held constant.

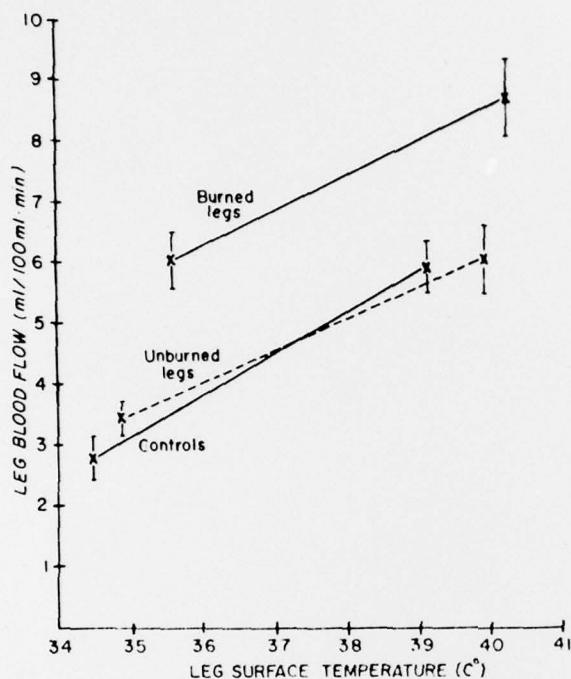


Fig. 4. Peripheral vascular response to local heating. Leg surface temperature was increased 5°C for 30 minutes. Burn wound vasculature has some basal tone which responds appropriately to changes in local temperature.

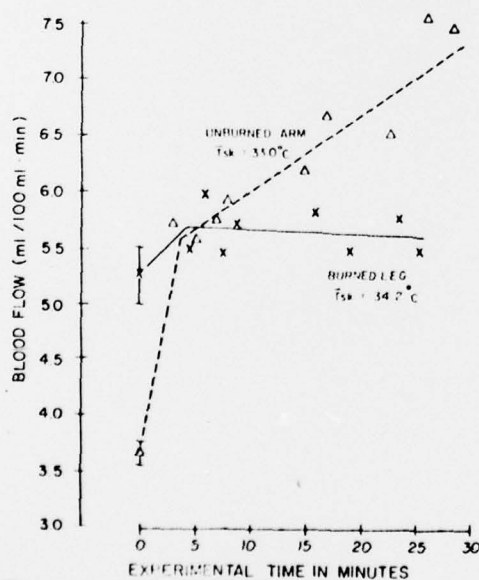


Fig. 5. Peripheral vascular response to indirect heating. Limb temperatures held constant and core temperature increased 0.5°C by 30 minutes of radiant heat. Reflex cutaneous vasodilation only evident in the uninjured limb.

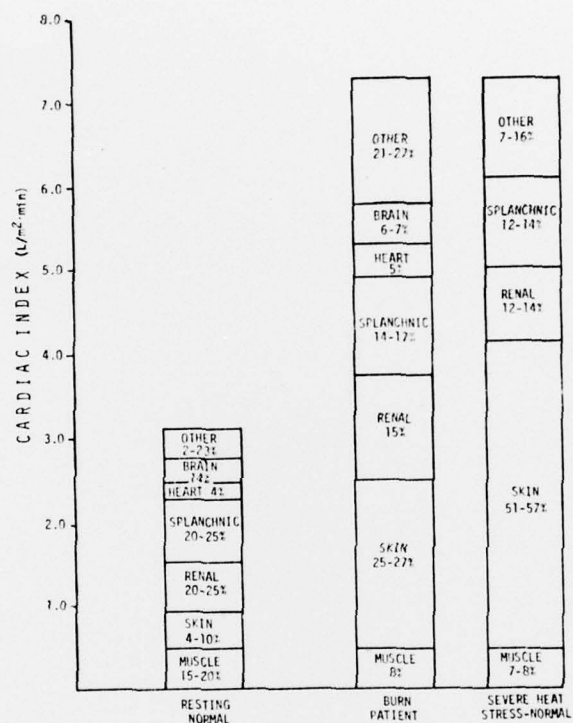


Fig. 6. Estimated changes in distribution of the cardiac index following a 50% total body surface burn. The major increase in skin blood flow is directed to the burn wound. The greater skin blood flow in heat stressed normals occurs from a fully dilated cutaneous vascular bed while unburned skin in the patient is vasoconstricted.